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ORIGINAL ARTICLE

The effects of serum concentration of androgens, LH and IGF1 in early follicular phase on follicular growth parameters and pregnancy rate

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KEYWORDS

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Abstract Objective: Many studies have showed the role of androgens on the follicular maturation. The present study investigated the effect of serum concentration of androgens, LH and IGF1 in the early follicular phase on the results of the ovulation induction (I/O) and intrauterine insemination (IUI) cycles. Materials and methods: This prospective observational cross-sectional study was carried out in the infertility department of a university hospital in Tehran, Iran. The case's selection was based on the inclusion and exclusion criteria and was nonrandomized. 59 patients under the age of 45 who were candidate for induction ovulation (I/O) or intrauterine insemination were included. The inclusion criteria consist of infertility for at least one year and at least one open tube in HSG. Patients were excluded if they had polycystic ovary syndrome (PCOS) or endometriosis. The serum concentration of androgens (testosterone, dehydroepiandrosterone and androstenedione), LH and IGF1 was measured on the third day of menstruation. Clomiphene and human menopausal gonadotropin (HMG) were drugs of induction ovulation. Human chorionic gonadotropin (HCG) was injected when there was at least one follicle with the size of (18 mm). IUI was done 36 h later for eligible patients and the relation of concentration of androgens, LH and IGF1 with follicular growth parameters and pregnancy rate was analyzed. Results: There was not any statistical significant link between the number and size of follicles with levels of free testosterone, dehydroepiandrosterone, androstenedione, IGF1 and LH. There was not any statistical significant link between the number

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of follicles in the ovaries and levels of testosterone ($P = 0.090$ and $r = 0.223$), dehydroepiandrosterone ($P = 0.642$ and $r = 0.062$) and androstenedione ($P = 0.526$ and $r = 0.084$), IGF1 ($P = 0.470$ and $r = 0.096$) and LH ($P = 0.446$ and $r = 0.102$). There was not any statistical significant link between the mean follicular size with levels of testosterone ($P = 0.822$ and $r = 0.03$), dehydroepiandrosterone ($P = 0.733$ and $r = 0.045$) and androstenedione ($P = 0.526$ and $r = 0.084$), IGF1 ($P = 0.799$ and $r = 0.034$) and LH ($P = 0.626$ and $r = 0.065$). Beta Human chorionic gonadotropin (beta-hCG) was positive in 11 patients (18.6%) and negative in 48 patients (81.4%). Serum level of androgen profile, LH and IGF1 in positive BHCG group was lower than negative BHCG group but was not significantly different. Conclusion: It seems that in women who were not affected by PCO, concentration of free testosterone, dehydroepiandrosterone, androstenedione, IGF1 and LH in early follicular phase was not related to follicular growth parameters and pregnancy rate.

1. Introduction

The androgens as the precursors of estrogens in ovary have the important role in follicular maturation and ovulation. This effect may result in assuming them as the future generation of drugs for induction ovulation. But the exact knowledge of the androgen effects on human follicle maturation does not exist and yet has remained controversial (1,2).

QIN and his colleagues evaluated the baseline level of testosterone during the follicular phase as a predictor of ovarian response and IVF results, and 1260 Chinese women without endometriosis or polycystic ovarian syndrome who underwent IVF cycle, were evaluated. These patients were divided into two groups with limited ovarian reserve (base FSH levels over IU/L 10) (187 patients) and normal ovarian reserve (base FSH levels less than or equal IU/L 10) (1073 people). The results of this study showed that baseline testosterone level in women with limited ovarian reserve is a predictor of large follicles and pregnancy (3).

In a study that was conducted in 2011 by Gleicher and colleagues, he examined the role of androgens in follicular maturation and ovulation in infertile patients. According to the results of this study that reviewed 217 published articles between 2005 and 2011, androgen had an important role in follicular maturation and fertility of women (1). A study conducted by Meldrum and his colleagues examined the role of decreased androgens in the ovarian response to stimulation in older women. Based on these results, increased serum levels of IGF-1, exogenous and local testosterone in the ovaries were associated with increased ovarian response to gonadotropins (4).

Gleicher also investigated the conversion rate of dehydroepiandrosterone in diminished ovarian reserve patients and concluded that women who conceived had a better convention rate (2). Also because insulin growth factor-1 (IGF-1) is essential for the conversion of androgens to estrogens this study aimed to evaluate the basal concentration of different types of androgens, LH and (IGF-1) in the early follicular phase of the cycle on ovulation induction (I/O) and intrauterine insemination (IUI) results.

2. Material and methods

This prospective observational cross-sectional study was carried out in the infertility department of a university hospital in Tehran, Iran. This study was approved by ethics committee of Iran University of Medical Sciences. The case's selection was based on the inclusion and exclusion criteria and was nonrandomized. All cases provided written informed consent before study registration. 59 patients under the age of 45 who were candidate for induction ovulation (I/O) or intrauterine insemination were included. The inclusion criteria consist of infertility for at least one year and at least one open tube in HSG. Patients were excluded if they had PCOS or endometriosis. Blood samples were collected on the third day of menstruation and the serum level of androgens (testosterone, dehydroepiandrosterone and androstenedione), LH and IGF1 was measured. Also, all the patients underwent transvaginal ultrasound to record and collect the base data. Clomiphene and human menopausal gonadotropin (HMG) were drugs of induction ovulation. Sonographic monitoring was started from the ninth day of the cycle. HCG was injected when there was at least one follicle with the size of (18 mm). IUI was done 36 h later for eligible patients and the records were collected by completing a checklist. The relation of concentration of androgens, LH and IGF1 with follicular growth parameters and pregnancy rate was analyzed by using SPSS software. Chi-2 test and Independent sample *t*-test were used to examine the relation between variables.

3. Results

59 patients entered the study that had a mean age of 32.1 ± 5.3 years, with the minimum and maximum ages of 20 and 44 years old. The mean and standard deviation of height, weight and body mass index of patients who entered the study were 158.3 ± 13.3, 66.6 ± 16.5 and 25.4 ± 4.9 respectively. The mean and standard deviation of the infertility periods were 49.1 ± 36.3 months that the lowest and highest were 12 and 156 months, respectively. BHCG was positive in 11 patients (18.6%) and negative in 48 patients (81.4%). Table 1 shows the relationship between level of androgen profiles, LH and IGF1 and BHCG results.

There was not any statistically significant link between the number of follicles in the ovaries and levels of testosterone ($P = 0.090$ and $r = 0.223$), dehydroepiandrosterone ($P = 0.642$ and $r = 0.062$) and androstenedione ($P = 0.526$ and $r = 0.084$), IGF1 ($P = 0.470$ and $r = 0.096$) and LH ($P = 0.446$ and $r = 0.102$). There was not any statistically

Table 1 Level of androgen profiles, LH and IGF1 and BHCG results.

	Positive BHCG	Negative BHCG	*P*
Testosterone (nanomole/liter)	0.95 ± 0.93	0.95 ± 1.1	0.170
DHEA (nanomole/liter)	0.31 ± 1.1	0.6 ± 1.3	0.280
Androstenedione (nanomole/liter)	0.42 ± 1	0.5 ± 1.1	0.575
LH (IU/L)	2.2 ± 1.5	2.8 ± 2.6	0.178
IGF1 (nanogr/milliliter)	21.8 ± 113.4	34.7 ± 125.4	0.632
Mean follicular size	2.9 ± 15.15	2.1 ± 14.36	0.168

Table 2 Comparison of androgen levels, LH and IGF1 by age group.

	Younger than 35 years	Older than 35 years	*P*
Testosterone (nanomole/liter)	0.99 ± 1.09	0.93 ± 1.03	0.859
DHEA (nanomole/liter)	0.56 ± 1.2	0.79 ± 1.4	0.708
Androstenedione (nanomole/liter)	0.53 ± 1.1	0.37 ± 1.1	0.331
LH (IU/L)	2.9 ± 2.3	2.4 ± 2.8	0.261
IGF1 (nanogr/milliliter)	30.2 ± 122.2	39.5 ± 125.4	0.382

Table 3 LH/IGF1, testosterone/IGF1, ASD/IGF1 and DHEA/IGF1 ratios in positive and negative BHCG groups.

	Negative BHCG	Positive BHCG	*P*
LH/IGF1	0.025 ± 0.021	0.022 ± 0.014	0.173
Testosterone/IGF1	0.005 ± 0.008	0.004 ± 0.007	0.572
ASD/IGF1	0.002 ± 0.009	0.001 ± 0.009	0.930
LH/IGF1	0.005 ± 0.010	0.001 ± 0.009	0.508

significant link between the mean follicular size with levels of testosterone ($P = 0.822$ and $r = 0.03$), dehydroepiandrosterone ($P = 0.733$ and $r = 0.045$) and androstenedione ($P = 0.526$ and $r = 0.084$), IGF1 ($P = 0.799$ and $r = 0.034$) and LH ($P = 0.626$ and $r = 0.065$).

The patients were divided into two groups based on their age, younger than 35 years and older than 35 years, and the androgen levels, LH and IGF1 were compared between the two groups which is shown in Table 2.

The number of follicles also was not significantly different between two age groups (4.12 ± 4 v/s 2.8 ± 3.7 $P = 0.341$).

In patients younger than 35 years, Serum level of Testosterone ($P = 0.374$), dehydroepiandrosterone ($P = 0.353$), androstenedione ($P = 0.652$), IGF1 ($P = 0.805$) and LH ($P = 0.611$) in positive BHCG group was lower than negative BHCG group but not significantly different. In patients older than 35 years, Serum level of Testosterone ($P = 0.235$), dehydroepiandrosterone ($P = 0.706$), androstenedione ($P = 0.941$), IGF1 ($P = 0.784$) and LH ($P = 0.118$) in positive BHCG group was lower than in negative BHCG group but not significantly different. Table 3 compares LH/IGF1, Testosterone/IGF1, ASD/IGF1 and DHEA/IGF1 ratios by the results of BHCG.

4. Discussion

The role of androgens in follicular development and ovulation is controversial. The present study cannot show any positive or negative relationship between the concentration of selective androgens (free testosterone, dehydroepiandrosterone, androstenedione), LH, IGF-1 and androgens/IGF-1 in the early follicular phase and the follicular growth parameters and the pregnancy rate.

Environmental endocrine system plays the main role in oocyte maturation and ovulation. The oocytes with lower quality were seen in women with PCO faced with hyperandrogenism. Okon showed that increase in plasma androgens causes recurrent abortion (5). Horie also reported that androgens with detrimental effects on endometrial development can cause raise of miscarriage (6).

In the past few years, it was assumed that androgens have a positive role in follicle development. Androgens affect follicle maturation from very early stages and stimulate the transition from primary to secondary follicle (7). Weil suggested a primary importance for androgens, especially in the early stages of follicle maturation (8).

Gervásio review indicates that during the early and intermediate stages of follicular maturation, the androgens locally produced by the developing follicles, control the follicle transition from the reserve pool to the growth pool and also control the promotion of subsequent follicle development. The fall in AR expression in mature follicles reduces the action of androgens which is a key event during the processes of follicular selection and atresia (9). Androgens may affect folliculogenesis directly via androgen receptors (ARs) or indirectly through aromatization to estrogen. ARs are highly expressed in the granulosa and theca cells of early stage follicles and are slightly expressed in mature follicles. Short-term androgen exposure augments the FSH receptor expression in the granulosa cells of developing follicles and controls the follicular cell proliferation and differentiation. AR activation also increases insulin-like growth factor (IGF-1) in the granulosa and theca cells of growing follicles, and in the oocytes of primordial follicles and facilitates the IGF-1 actions in both follicular recruitment and subsequent development (9).

But about the role of androgens in subsequent follicular development, Gleicher review showed the effects of androgens in improving human ovulation induction and demonstrated the essential contribution of androgens to normal follicle maturation. He suggested that some androgens, such as testosterone (T) and dehydroepiandrosterone (DHEA), are effective in improving functional ovarian reserve (FOR) in women with diminished ovarian reserve (DOR), but others may have opposite effects (1).

Sun evaluated basal testosterone (T) levels in women undergoing in vitro fertilization (IVF) cycles. He showed basal T level positively correlated with ovarian reserve function, number of mature follicles and total gonadotropin dose but couldn't predict IVF pregnancy outcome. He concluded that basal T level can be used as a good predictor for ovarian response and also as a marker to predict FSH dosage (10).

Supplementation with dehydroepiandrosterone (DHEA) in women with DOR improves IVF cycle outcomes and pregnancy chances which shows the androgen effects on human follicle maturation. But, how DHEA causes these effects has remained undetermined.

Gleicher studied the androgen conversion rate after supplementation with dehydroepiandrosterone in patients with diminished ovarian reserve who were candidate for in vitro fertilization. He concluded that women who conceived had a better conversion rate (2).

IGF-1 stimulates the DNA synthesis, steroidogenesis, and aromatase activity (11). It has a critical role in the conversion of androgens and the building of a suitable environment for the ovum. Our result does not show any difference in IGF-1 and also androgens/IGF-1 in the conceived group. Androgens/IGF-1 was evaluated because it can be a factor in aromatization and optimal androgen environment. However we couldn't evaluate the local bioactivity of the androgens which was the limitation of our study. It is suggested that further study must focus on factors that affect conversion and bioactivity of androgens.

Conflict of interest

The authors declared that there is no conflict of interest.

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